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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,146	01/29/2002	Alexander Vainstein	10980-017001	1751
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Fish & Richardson 225 Franklin Street Boston, MA 02110-2804				
EXAMINER KOROMA, BARBA M				
ART UNIT			PAPER NUMBER	
1638				

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/914,146

Applicant(s)

VAINSTEIN ET AL.

Examiner

Barba M. Koroma

Art Unit

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-40 is/are pending in the application.
- 4a) Of the above claim(s) 27 and 28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-26 and 29-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 January 2002 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner. [See item 3 in office action]
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 4/15/02.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group IV, claims 21-26 in the paper filed on January 29, 2002 is acknowledged. Claims 21-26 and new claims 29-40 have been examined in this Office action. Non-elected claims 1-20, 27, and 28, are withdrawn from consideration.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 USC 119/120 as follows: it is noted that this application appears to claim subject matter disclosed in prior PCT application No. 60/121, 239 filed on 2/22/1999. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or the application data sheet (37CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 USC 119(e) or 120. See 36 CFR 1.78(a).

Drawings

3. The specifications describes figures 14a, 14b, 14c, 14d and 14e as showing flower color modification of *anti-fht* transgenic carnation. However, the images observed for said figures are in black and white. Correction is requested.

Information Disclosure Statement

4. The following objections are directed to the Information Disclosure Statement (IDS) filed with the application for failing to provide complete citation of the reference as required on PTO-1449:

The IDS is objected to for failing to state the year and source of publication for the following non-patent literature references:

i. Zuker et al. (wounding by bombardment yields efficient *Agrobacterium*-mediated transformation of carnation).

Specification

5. The specification is objected to for a spelling error of the word "trasfected" (line 3, page 30). Correction is requested.

Claim Rejections – 35 USC 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 39 recites the term "leave." It is not clear whether applicant is referring to a leaf, leaves, or leave. Correction is requested.

7. Claims 25 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The strand complimentary to a coding sequence of a nucleic acid is the anti-sense strand. This could be a DNA or RNA molecule depending on whether the complimentary strand is a DNA or RNA strand. It is not clear whether Applicant is referring to a complimentary DNA, RNA. Clarification is requested.

8. Claims 29-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 lists the steps for making a transgenic shoot. However, the parent claim is directed to controlling fragrance of a plant (step (e) of claim 29) not a shoot. It is suggested that the claim be amended to indicate the transformation of a plant stating how fragrance is controlled in the resulting transgenic plant.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 21 and 29-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing fragrance of a plant comprising expressing an *fht* cDNA in anti-sense orientation in transgenic plants, it does not reasonably provide enablement for controlling fragrance in any other manner. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of undue experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are broadly drawn to a method for controlling fragrance by modulating gene expression in the anthocyanin-biosynthetic pathway of a plant. The specification teaches preparation of stem cuttings of carnation plants, wounding shoot explants by microprojectile bombardment, co-cultivating the wounded explants with *Agrobacterium* comprising the DNA molecule under conditions of exposure to dark followed by light, excising shoots from the cultivated wounded explants, removing the leaves from the shoots, and culturing the leaves to obtain transgenic shoots transformed with a DNA molecule (item numbers 1-6, pages 12-16).

The specification provides guidance for isolation and cloning of carnation *fht* cDNA by reverse transcription of poly(A)⁺ RNA using specific primers to the sequence in GenBank (X70378). This fragment was subcloned in anti-sense orientation between the CaMV35S promoter and *nos* terminator in pJD 330. An XbaI fragment from pJD-anti-*fht* was then cloned into the binary vector pCGN1559 to create pAM-anti-*fht*. The gene construct was transferred to

carnation cv. Eilat by co-cultivation of stem explants with *Agrobacterium tumefaciens* AGLO-containing pAM-anti-*fht* (material and methods, p29-30). Applicants teach Northern blot and RT-PCR analysis showing dramatic reduction of *fht* transcript in transgenic carnation plants compared to controls (page 32, last paragraph). The specification also indicates that field tests of transgenic plants showed more fragrance in plants with a corresponding strong reduction in anthocyanin accumulation, compared to non-transformed or GUS-transgenic controls (2nd paragraph, p30). Applicants teach that GC-MS headspace characterization of volatiles produced in transgenics show a representation of terpenoid *trans*-caryophyllene, fatty acid derivative hexanoic acid, and the benzoic acid derivative methylbenzoate (3rd paragraph, page 33).

The specification fails to provide guidance for a method(s) of controlling fragrance of any plant other than by decreasing *fht* gene expression by expression of an *fht* encoding sequence in anti-sense orientation. The specification does not teach the modulation of anthocyanin biosynthetic pathway genes via use of anti-sense molecules, in such a manner as to result in both upward and downward emission of fragrance in carnation plants. The specification does not teach specific role(s) and or mechanism(s) associated with the control of fragrance in carnation by anthocyanin biosynthetic pathway gene(s). Furthermore, the specification does not teach a method of changing fragrance from one form to another. The specification does not provide guidance concerning proteins or other factors that regulate anthocyanin biosynthetic pathway genes. Furthermore, examples of such regulators are lacking in the prior art. It would require undue experimentation by one skilled in the art to characterize all anthocyanin biosynthetic pathway

genes in order to determine for each the ligands, co-factors, and optimal conditions necessary for their action in controlling fragrance in carnation.

Given the breadth of the claims, the lack of guidance and working examples, the unpredictability of the art as discussed above, one skilled in the art would require undue experimentation to make and use the claimed invention.

Claim Rejections - 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 21, 23, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Van der Krol (June 1988. Nature. Vol 333. p866-869).

The claims are broadly drawn to modulation of the expression of one or more genes in the anthocyanin-biosynthetic pathway of a plant.

Van der Krol et al teach the inhibition of chalcone synthase, an anthocyanin-biosynthetic pathway gene by transgenic expression of a chalcone synthase cDNA in anti-sense orientation.

Van der Krol's conclusion that secondary metabolism in plants can be manipulated using transgenic plants that constitutively synthesize anti-sense RNA is based on the inhibition of flower pigmentation by anti-sense inhibition of chalcone synthase shown in their study. As an

anthocyanin biosynthetic pathway gene, chalcone synthase inhibition inherently altered fragrance in the transgenic plants taught by Van der Krol et al, absent evidence to the contrary.

11. Claims 21, 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Holton et al (1993, PCT/AU93/00127).

The claims are drawn to a method of controlling or modulating the expression of anthocyanin biosynthesis pathway gene, flavonoid 3-hydroxylase (*fht*), using anti-sense molecules to produce enhanced fragrance in transgenic carnation plants.

Holton et al teach the isolation and cloning of cDNA encoding the anthocyanin synthetic pathway enzyme, flavonoid 3'-hydroxylase (*fht*) derived from petunia and other plants (claims 1-5, 7-12, 14-24, 26-29, 31-37). The reference teaches further a method of producing a genetically modified plant (claim 40) also referred to as a transgenic plant or active mutants or derivatives thereof (claims 31-39, 43-54), comprising stably transforming a cell with a nucleic acid molecule which comprises a sequence of nucleotides encoding or complimentary to a sequence encoding said flavonoid 3'-hydroxylase gene or derivative or part thereof introduced in to the plant cell (claims 40, 47). Reverse transcribed RNA from carnation petals were PCR-amplified and cloned into a binary vector (page 22, 26, specification). *Agrobacterium tumefaciens* containing the binary vector was co-cultivated with petunia leaf discs under a 16h photoperiod (cool white fluorescent light) (page 30-31, specification). Transgenic plants assayed for 3'-hydroxylase by Southern blotting showed noticeable color variations (page 33, specification). Since Holton et al teaches anti-sense inhibition of flavonoid 3'-hydroxylase (*fht*), alteration of fragrance in the transgenic plants is inherent.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. Claims ^{-16, 29-40}21-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holton et al (1993, PCT/AU93/00127), and further in view of Lu et al (1991. Bio/Technology. Vol. 9 p864-868) and Bidney et al (1992. Plant Molecular Biology. 18(2). 301-313).

The claims are broadly drawn to modulation of anthocyanin-biosynthetic pathway gene(s) expression in a transgenic plant by anti-sense inhibition. A transgenic carnation plant is produced by wounding stem explants by tungsten particle microprojectile bombardment accelerated at a pressure of 1300-2000 psi and at a distance of 3-12cm and then co-cultivating said wounded explants with *Agrobacterium* comprising DNA molecules in a medium supplemented with α -naphthalene acetic acid (NAA) and 1-phenyl-3(1,2,3-hiadiazol-5-yl)-urea and 6-nenzylaminopurine under conditions of light and dark; excising a shoot from cultivated wounded plants, and culturing a leaf from said explant to produce a transformed plant.

Holton et al teach anti-sense inhibition of flavonoid 3'hydroxylase (*fht*) in petunia (see discussion above). The reference also indicates that the same method can be practiced in carnation (page 42, claim 12; page 22, last paragraph).

Holton et al does not teach transgenic carnation plants.

Lu et al (1991. Bio/Technology. vol 9. p864) teach the transformation of carnation (*Dianthus caryophyllus*). The reference teaches stem (or shoot) segments and leaf explant regeneration (page 865, second paragraph) of carnation tissue co-cultivated with *Agrobacterium*, in medium supplemented with α -naphthalene acetic acid (NAA), 6-benzylaminopurine (BAP), and 2,4-dichlorophenoxyacetic acid (experimental protocol, page 867), under cool fluorescent light of 16h photoperiods (second paragraph, page 867).

Bidney et al (1992) teach a method of transformation of tobacco and sunflower plants involving co-cultivation of apical meristems wounded by tungsten particle microprojectile bombardment (page 303). Leaves bombarded with particles were then inoculated with *Agrobacterium*. After 72h *Agrobacterium* treatment of particle-bombarded tobacco leaves and sunflower meristems, all material was transferred to appropriate medium and subjected to assays to confirm transformation.

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made to apply the method of inhibiting *fht* gene expression of Holton et al in carnation plants. It would have been obvious to introduce the *fht* anti-sense gene of Holton et al into carnation plants using an applicable transformation method such as taught by Lu et al.

One would have been motivated to apply the method of Holton et al to carnation plants given the suggestion of Holton et al that the methods applied to petunia can be applied to carnation. It would have been obvious to further modify the method of producing the transgenic carnation plants by wounding carnation tissue by microprojectile bombardment prior to

Art Unit: 1638

inoculation with *Agrobacterium*, as taught by Bidney et al. One would have been motivated to do so because Bidney et al teach that *Agrobacterium* transfection of microprojectile-wounded tissue increases *Agrobacterium* transformation efficiencies at least a hundred-fold (page 310, lines 1-4).

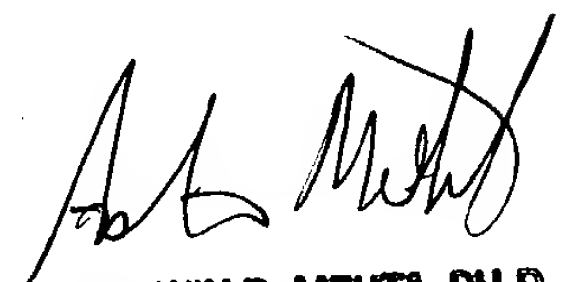
The choice of particles (including tungsten particles), the pressure at which they are accelerated (including 1300-2000 psi), and the distance to the target (including 3-12cm) were optimization of process parameters.

Contact Information

12. Any inquiry concerning this or earlier communications from the Examiner should be directed to Barba M. Koroma, whose telephone number is 571-272-0899. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

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